The co-occurrence of depression and anxiety with alcohol use disorders

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2012

CHAPTER 6

HEAVY ALCOHOL USE, RATHER THAN ALCOHOL DEPENDENCE, IS ASSOCIATED WITH DYSREGULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND THE AUTONOMIC NERVOUS SYSTEM

ABSTRACT

Background | Heavy alcohol use as well as alcohol dependence (AD) have been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis and the autonomic nervous system (ANS). However, the relative contribution of alcohol use and AD is unclear.

Methods | Baseline data were derived from 2,947 persons of the Netherlands Study of Depression and Anxiety (NESDA), including non-drinkers (n=498), moderate drinkers (n=2,112) and heavy drinkers (n=337). We also distinguished between persons with no lifetime DSM-IV AD (n=2,496), remitted AD (>1 year; n=243), and current AD (≤1 year; n=208). ANS measures included ECG-based heart rate (HR), respiratory sinus arrhythmia (RSA, high RSA reflecting high cardiac parasympathetic control) and pre-ejection period (PEP, high PEP reflecting low cardiac sympathetic control). HPA-axis measures included the cortisol awakening response (area under the curve with respect to the ground [AUCg] and increase [AUCi]), evening cortisol and a 0.5 mg dexamethasone suppression test, all measured in saliva.

Results | Heavy drinkers showed higher basal cortisol levels (AUCg: p=.02; evening cortisol: p=.006) and increased cardiac sympathetic control (higher HR: p=.04; lower PEP: p=.04) compared to moderate drinkers. Persons with current or remitted AD did not differ from persons without lifetime AD on any of the HPA-axis or ANS indicators (all p>.33). Similar patterns of HPA-axis and ANS activity across alcohol use groups were found in persons with and without lifetime AD.

Conclusions | Our findings suggest that current heavy alcohol use, rather than current or remitted AD, is associated with hyperactivity of the HPA-axis and increased cardiac sympathetic control.

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Published in Drug and Alcohol Dependence 2011; 116:170-176.

INTRODUCTION

Heavy alcohol use and alcohol dependence (AD) have been associated with a wide range of physiological, psychological and behavioral problems. For example, heavy drinkers and persons with AD have an increased risk of cardiovascular disease (Corrao et al., 2000) and cancer (Bagnardi et al., 2001; Boffetta and Hashibe, 2006) as well as depressive and anxiety disorders (Burns and Teesson, 2002; Swendsen et al., 1998). In addition, alcohol use has been linked to harmful behavioral consequences such as aggressive behavior, crime and unintended injuries (Gmel and Rehm, 2003) and AD is characterized by a loss of control over the alcohol use (American Psychiatric Association, 2000). In an attempt to comprehend the common underlying mechanisms associating alcohol with these various problems, Thayer and Lane (Thayer et al., 2006) proposed the neurovisceral integration model (Thayer and Lane, 2000), comprising the hypothalamic-pituitary-adrenal (HPA)-axis and the autonomic nervous system (ANS). They hypothesized that alcohol ingestion is directly associated with both stress systems, following which chronic activation, as in AD, may result in impaired inhibitory control (Thayer et al., 2006).

The HPA-axis has a key role in normal physiological processes and in adaptation to stress (Selye, 1936). It is responsive to the basic motivational processes, such as seeking food, ingestion of nutrients and threats to well being (Lovallo, 2006). Alcohol use stimulates the HPA-axis and, with that, causes stress-like cortisol responses resulting in elevated basal cortisol levels (Gianoulakis et al., 2003; Thayer et al., 2006) and an increased cortisol awakening response (Adam et al., 2006; Badrick et al., 2008). Although heavy alcohol use has been associated with hyperactivity of the HPA-axis, AD has been linked to a blunted stress response for at least four weeks post-withdrawal (Bernardy et al., 1996; Errico et al., 1993; Lovallo et al., 2000; Sinha et al., 2009). However, these studies in persons with AD have been restricted to those who are abstinent from alcohol and, therefore, could not clarify the relative contributing role of alcohol use and AD to activity of the HPA-axis. A further limitation of these previous studies is that only inpatients severely dependent on alcohol were included.

Studies have also provided evidence for a role of the ANS in the pathophysiology of alcohol use and AD. The ANS allows for flexible and adaptive behavior across challenging situations due to its interplay between the sympathetic nervous system (excitatory processes) and parasympathetic nervous system (inhibitory processes) (Thayer and Lane, 2000). High parasympathetic control is associated with adequate modulation of affect and emotion and increased impulse control (Allen et al., 2000), whereas low parasympathetic control is associated with affect dysregulation as in persons with depressive and anxiety disorders (Thayer et al., 1996; Thayer et al., 1998). Previous studies have shown that alcohol use causes increased sympathetic control (Ohira et al., 2009; Ryan and Howes, 2002) and an acute reduction in parasympathetic control (Reed et al., 1999; Vaschillo et al., 2008; Weise et al., 1986). Persons with AD also showed a decrease in parasympathetic control and an increase in sympathetic control during acute alcohol withdrawal and during alcohol abstinence up to 4 weeks (Bar et

al., 2006; Ingjaldsson et al., 2003; Kahkonen and Bondarenko, 2000; Rechlin et al., 1996; Thayer et al., 2006). Because studies associating ANS with alcohol use are restricted to heavy drinkers without AD, and studies on AD only included non-drinkers with severe AD, much is still unclear about the unique contribution of alcohol use and AD to sympathetic and parasympathetic control of the heart.

To our knowledge, this study is the first in examining the HPA-axis as well as ANS in a large sample of persons with no, remitted, and current AD who also differ in the amount of alcohol use (no, moderate, heavy alcohol use). Consequently, we are able to assess the relative contribution of alcohol use and AD to dysregulation of both stress systems. In order to examine HPA-axis and ANS indicators in a broad range of alcohol dependent persons, persons with a DSM-IV diagnosis of AD are not restricted to the specific subgroup of severely addicted inpatients as in previous studies. In addition, the current study is sufficiently powered to examine confounding by socio-demographics, health indicators and depressive or anxiety disorders.

METHODS

Study sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008), an ongoing longitudinal cohort study among 2,981 adults (18-65 years), from which 94.8% were of North-European ancestry. Participants were recruited from the community (19%), from primary care (54%) through a screening procedure conducted among 65 General Practitioners, and from specialized mental health care (27%) when newly enrolled at one of the 17 participating mental health centers. At the 4-hour baseline assessment (2004-2007), including written questionnaires, a face-to-face interview, a medical exam, an experimental computer task and blood collection, extensive information was gathered about demographic, clinical, psychosocial, genetic and biological characteristics. Information on ANS indicators was assessed during the face-to-face interview at one of the clinic sites, whereas participants collected their saliva samples for information on HPA-axis indicators at home shortly after the interview. Participants were compensated with a small incentive (gift certificate of 15 euro and payment of travel costs) for their time and cooperation. A detailed description of the NESDA study design and sampling procedure can be found elsewhere (Penninx et al., 2008). The research protocol was approved by the Ethical Committee of participating universities and all participants provided written informed consent.

Pregnant or breastfeeding women (n=27) and persons on corticosteroids (n=165) were excluded for HPA-axis activity measurement, because of interference of their condition with HPA-axis activity. Another 742 persons did not return (sufficient) saliva samples, leaving a sample of 2,047 persons (68.7%). Persons with valid data on HPA-axis activity tended to be more often men (34.7% versus 32.3%, p=.07), were older (43.3 versus 38.8 years, p<.001) and more educated (12.4 versus 11.7 years, p<.001) than excluded persons (n=934). Included persons did not differ from excluded persons in the

percentage of heavy drinkers (11.3% versus 11.7%; p=.80), but included persons showed a slightly lower percentage of non-drinkers (15.5% versus 20.2%; p=.001) and a slightly higher percentage of moderate drinkers (73.2% versus 68.1%; p=.004). Included persons had a lower prevalence of current AD (6.4% versus 8.5%, p=.05) and a higher prevalence of no AD (85.7% versus 82.1%; p=.01) than excluded persons.

With regard to the ANS analyses, 118 persons were excluded because no ANS data were available, leaving a sample of 2,863 (96.0%) persons. Persons with valid ANS data were slightly younger (41.8 versus 44.0 years, p=.06), but did not differ with respect to gender (p=.64), education (p=.66), alcohol use (p=.13) and AD status (p=.65) from excluded persons.

Alcohol variables

Alcohol use - Alcohol use was assessed by two items of the Alcohol Use Disorder Identification Test (AUDIT) questionnaire (Babor et al., 1992) concerning the average frequency of drinking and the amount of drinks on a typical drinking day in the past year. From these items, we derived the average amount of alcoholic drinks/day, in which one drink refers to one glass of a drink containing alcohol. We, subsequently, distinguished between non-drinkers (0 drinks/day), moderate drinkers (men: ≤3, women: ≤2 drinks/day), and heavy drinkers (men: >3, women: >2 drinks/day), based on general guidelines that are used in health organizations in the Netherlands (Stuurgroep Multidisciplinaire Richtlijnontwikkeling GGZ, 2009) and in other studies on this topic (e.g., Gianoulakis et al., 2003).

AD status - A diagnosis of alcohol dependence was established with the Composite International Diagnostic Interview (CIDI), version 2.1 (World Health Organization, 1997), which classifies diagnoses according to DSM-IV criteria (American Psychiatric Association, 2000). The CIDI is reliable and valid in assessing AD (Üstün et al., 1997) and was administered by specially trained research staff. A distinction was made between no AD, remitted AD (lifetime AD but not in the last 12 months) and current AD (meeting AD criteria in the last 12 months).

Hypothalamic-pituitary-adrenal (HPA) axis

As described in more detail elsewhere, participants were instructed to collect saliva samples at home on (Vreeburg et al., 2009b; Vreeburg et al., 2009a) a regular (preferably working) day, shortly after the interview. The median time between the interview and saliva sampling was 9.0 days (25th-75th percentile: 4-22). Saliva samples were obtained using Salivettes (Starstedt, Germany) at seven time points. The cortisol awakening response (CAR) includes four sampling points: one at awakening (T1) and the other three 30 (T2), 45 (T3) and 60 (T4) minutes later. Two evening cortisol values were collected: one at 22h00 (T5) and one at 23h00 (T6). Dexamethasone suppression was measured by cortisol sampling the next morning at awakening (T7) after ingestion of 0.5 mg dexamethasone directly after the saliva sample at 23h00. Samples were stored in refrigerators and returned by mail. After receipt, Salivettes were centrifuged at 2000g

for ten minutes, aliquoted and stored at -80 °C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switzerland), as described in Van Aken et al. (Van Aken et al., 2003). The functional detection limit was 2.0 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%. Data cleaning excluded values >2 SD above the mean (i.e. above 59.6-123.6 nmol/l for T1-T4, 40.9 nmol/l for T5, 59.8 nmol/l for T6 and 35.6 nmol/l for T7).

Cortisol awakening response - The area under the curve with respect to the ground (AUCg) and the area under the curve with respect to the increase (AUCi) were calculated using the formulas described by Pruessner (Pruessner et al., 2003). The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUCi is a measure of the dynamic of the cortisol awakening response. Both measures require all four morning samples (n=1,723).

Evening cortisol – The mean of the two evening measures was used to reflect evening cortisol level. At least one evening cortisol value was required (n=2,035).

Cortisol suppression test – We used a cortisol suppression ratio calculated by cortisol awakening on the first day (T1) divided by cortisol value at awakening the next day (T7) after ingestion of 0.5 mg Dexamethasone the evening before. Only those persons who reported that they had ingested dexamethasone, were included in these analyses (n=1,936).

Autonomic nervous system (ANS)

During their visit to the research centers, participants were requested to wear the Vrije Universiteit Ambulatory Monitoring System (VU-AMS; Vrije Universiteit, Amsterdam, the Netherlands). The VU-AMS is a light-weight portable device that records electrocardiograms (ECG) and changes in thorax impedance (dZ) from six surface electrodes placed at the chest and back of the participant (De Geus et al., 1995; Willemsen et al., 1996). With this device we could establish respiratory sinus arrhythmia (RSA), heart rate (HR), and pre-ejection period (PEP).

RSA - RSA reflects cardiac parasympathetic control (high RSA reflecting high parasympathetic control), and was obtained by combining the inter-beat interval time series with the filtered (0.1-0.4 Hz) dZ signal which corresponds to the respiration signal. RSA was obtained by subtracting the shortest inter-beat-interval (IBI) during heart rate acceleration in the inspirational phase from the longest IBI during deceleration in the expirational phase for all breaths (n=2,863).

HR - The interbeat interval time series was extracted from the ECG signal to obtain HR, as an indicator of both sympathetic and parasympathetic control over the heart (n=2,863).

PEP - PEP reflects cardiac sympathetic control (high PEP reflecting low sympathetic control) as the noradrenergic inotropic drive to the left ventricle and was obtained from the dZ/dt signal, ensemble averaged across one-minute periods time-locked to the R-wave of the ECG. PEP was defined as the interval from the B-point (upstroke) to the X-point (incisura) of the dZ/Dt signal (n=2,829).

Covariates

Sociodemographics, health and sampling factors as well as depression/anxiety-related characteristics were considered as covariates as they have been linked with alcohol use and/or alcohol dependence as well as with the HPA-axis and/or the ANS in previous studies. Socio-demographic factors included sex, age and years of education. Body mass index (BMI) was calculated as weight divided by length in meters squared. Physical activity was assessed with the International Physical Activity Questionnaire (Craig et al., 2003) and expressed in 1000 Metabolic Equivalent (MET)-minutes in the past week. Information about past and current smoking was obtained during the interview. Cardiovascular disease (including coronary disease, cardiac arrhythmia, angina pectoris, heart failure and myocardial infarction) and number of other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, chronic fatigue syndrome, intestinal disorders and ulcers) were ascertained by self-report. Furthermore, use of heart medication was assessed by drug container inspection of medication used in the past month and classified according to the World Health Organizations Anatomical Therapeutic Chemical (ATC) coding system. Both use of beta-blockers (ATC code C07, used at least 50% of the time) and use of other cardiovascular medication (ATC-codes C01 [cardiac therapy], C02 [antihypertensives], C03 [diuretics], C04 [peripheral vasodilators], C05 [vasoprotectives], C08 [calcium channel blockers] or C09 [agents acting on the renin-angiotensin system]) were ascertained. Diagnoses of DSM-IV remitted (lifetime but not in the last 12 months) or current (in the last 12 months) depressive (major depressive disorder and dysthymia) and anxiety (generalized anxiety disorder, social phobia, panic disorder and agoraphobia) disorders were established with the Composite International Diagnostic Interview (CIDI), version 2.1 (World Health Organization, 1997). Use of selective serotonin re-uptake inhibitors (SSRIs; ATC code N06AB), tricyclic antidepressants (TCAs; ATC code N06AA) and other antidepressants (N06AF and N06AX, mainly venlafaxine and mirtazapine) were also ascertained. Additionally, for analyses of cortisol measures, sampling factors that have been shown to influence cortisol measures by Vreeburg et al. (Vreeburg et al., 2009b), were included. Participants reported time of awakening and working status on the sampling day. Season was categorized into dark months (October through February) and months with more daylight (March through September). Average sleep duration during the last week was dichotomized into sleeping more or less than six hours a night.

Statistical analysis

Analyses were conducted using SPSS version 15.0 statistical software. All HPA-axis and ANS measures showed normal distributions except for the evening cortisol level and the cortisol suppression ratio, which were log transformed before analyses and back-transformed to report in tables and figures. Baseline characteristics were compared across groups based on alcohol use (no, moderate, heavy alcohol use) and AD status (no, remitted, current AD) using X^2-statistics for categorical variables and analysis of variance for continuous variables. To examine whether HPA-axis measures (i.e. AUCg,

AUCi, evening cortisol level and cortisol suppression ratio) and ANS measures (i.e. HR, RSA and PEP) differed across groups based on alcohol use (reference: moderate drinkers) and AD status (reference: no AD), we used analyses of (co)variance. Results of unadjusted analyses as well as adjusted analyses controlling for covariates are presented. In addition to separately relating the alcohol variables with HPA-axis and ANS measures, we also examined the relative contribution of alcohol use and AD status. Therefore, we tested whether the patterns of HPA-axis and ANS activity across the three alcohol use groups differed between persons with and without lifetime AD.

RESULTS

Sample

Mean age of the sample was 43.3 (SD=13.0) years and 65.3% were women. The distribution of alcohol use was as follows: 15.5% were non-drinkers (mean=0.0, SD=0.0 drinks/day; see **Table 1**), 73.2% were moderate drinkers (mean=0.8, SD=0.7 drinks/day) and 11.3% were heavy drinkers (mean=4.0, SD=1.8 drinks/day). Of the sample, 85.8% had no lifetime AD (mean=0.8, SD=1.1 drinks/day), 7.8% had remitted AD (mean=1,3, SD=1.8 drinks/day) and 6.4% had current AD (mean=2.8, SD=2.3 drinks/day). Most of the sample characteristics differed significantly between alcohol use groups and between diagnostic (AD) groups (see **Table 1**), indicating the need for statistical adjustment of differences in outcomes.

HPA-axis measures

Table 2 presents results from unadjusted and adjusted analyses, associating HPA-axis activity with alcohol use and AD status.

Cortisol awakening response (CAR): AUCg – Heavy drinkers had an increased AUCg compared to moderate drinkers in both unadjusted and adjusted analyses (adjusted: p=.02). No significant differences in AUCg were found between non-drinkers and moderate drinkers (adjusted: p=.75). Although persons with remitted and current AD had a higher AUCg compared to persons without AD in the unadjusted analyses (p=.08 and p=.04, respectively), these associations were not significant after adjustment for covariates (adjusted: p=.70 and p=.68, respectively).

Cortisol awakening response (CAR): AUCi – No significant associations were found between alcohol use levels or AD status and AUCi in the unadjusted or adjusted analyses.

Evening cortisol: In both unadjusted and adjusted analyses, heavy drinkers had an increased evening cortisol level compared to moderate drinkers (adjusted: p=.006), whereas non-drinkers did not differ from moderate drinkers (adjusted: p=.29). Evening cortisol levels were significantly higher among persons with remitted and current AD compared to persons without lifetime AD in unadjusted analyses (p=.01 and p=.006, respectively), but these differences were no longer significant after adjustment for potential confounders (adjusted: p=.67 and p=65, respectively).

Cortisol suppression ratio: In the unadjusted analyses, non-drinkers and heavy drinkers had a significantly decreased cortisol suppression ratio relative to moderate drinkers (p=.04 and p=.03, respectively), but the differences were no longer significant after adjustment for potential confounders (adjusted: p=.07 and p=.18, respectively). No significant associations were found between AD status and the cortisol suppression ratio in both unadjusted and adjusted analyses.

ANS measures

Results from both unadjusted and adjusted analyses associating alcohol use and AD status with ANS measures are also presented in **Table 2**.

Parasympathetic control: RSA – In the unadjusted analyses concerning alcohol use and RSA, we initially found an inverted U-curve in which non-drinkers and heavy drinkers had a significantly decreased RSA compared to moderate drinkers (both: p<.001). However, in the adjusted analyses this decrease only remained significant for non-drinkers (adjusted: p=.05) and not for heavy drinkers (adjusted: p=.37). No significant associations were found between AD status and RSA.

Parasympathetic/sympathetic control: HR – Adjusted analyses concerning alcohol use showed a U-curve in which non-drinkers and heavy drinkers had a significantly increased HR compared to moderate drinkers (adjusted: p=.006 and p=.04, respectively). Persons with a remitted and current AD did not significantly differ in HR from persons without AD in both unadjusted and adjusted analyses.

Sympathetic control: PEP – Although heavy drinkers did not significantly differ from moderate drinkers in the unadjusted analyses, PEP was significantly decreased in heavy drinkers in the adjusted analyses (adjusted: p=.04). Non-drinkers and moderate drinkers did not significantly differ in PEP in both unadjusted and adjusted analyses (adjusted: p=.08). Persons with remitted or current AD did not significantly differ in PEP from persons without AD.

Combining alcohol use and AD status

As HPA-axis and ANS measures were significantly related to alcohol use, and not to AD status, we therefore additionally studied whether the association with alcohol use was similar in persons with and without lifetime AD. **Figure 1** shows the results of adjusted analyses relating alcohol use to those HPA-axis (i.e. AUCg and evening cortisol) and ANS measures (i.e. RSA, HR, PEP) that showed a significant (p<.05) association with alcohol use in the previous analyses (see **Table 2**). The figures show similar patterns of the HPA-axis and ANS indicators across alcohol use groups in persons with and without a lifetime AD diagnosis. In addition, persons with and without lifetime AD did not significantly differ on any of the HPA-axis and ANS indicators within subgroups based on alcohol use (within non-drinkers: all p-values >.29; within moderate drinkers: all p-values >.41; within heavy drinkers: all p-values >.62). In sum, these findings confirm that it is indeed alcohol use, and not lifetime AD, that is driving the association.

Characteristic	Alcohol use				Alcohol dependence			
	No (n=498)	Moderate (n=2,112)	Heavy (n=337)	p[a]	No (n=2,496)	Remitted (n=243)	Current (n=208)	p[a]
Socio-demographics								
Female, n (%)	383 (76.9%)	1,350 (63.9%)	226 (67.1%)	<.001	1,723 (69.0%)	127 (52.3%)	109 (52.4%)	<.001
Age in years, mean (SD)	42.7 (12.8)	40.9 (13.1)	46.6 (12.3)	<.001	41.9 (13.2)	44.0 (11.9)	39.1 (12.2)	<.001
Education in years, mean (SD)	11.0 (3.2)	12.4 (3.2)	12.6 (3.5)	<.001	12.2 (3.3)	11.8 (3.3)	12.4 (3.3)	.13
Health and sampling factors								
Body Mass Index, mean (SD)	26.7 (5.8)	25.4 (4.9)	25.3 (4.5)	<.001	25.6 (5.0)	25.9 (4.9)	25.1 (4.8)	.21
Physical activity/1000 MET-min/week, mean (SD)	3.6 (3.2)	3.7 (3.0)	3.4 (3.0)	.18	3.7 (3.0)	3.7 (3.1)	3.6 (3.2)	.94
Smoking				<.001				<.001
No, n (%)	198 (39.8%)	585 (27.7%)	45 (13.4%)		785 (31.5%)	19 (7.8%)	24 (11.5%)	
Past, n (%)	138 (27.7%)	727 (34.4%)	120 (35.6%)		851 (34.1%)	91 (37.4%)	43 (20.7%)	
Current, n (%)	162 (32.5%)	800 (37.9%)	172 (51.0%)		860 (34.5%)	133 (54.7%)	141 (67.8%)	
Cardiovascular disease, n (%)	33 (6.6%)	122 (5.8%)	21 (6.2%)	.75	147 (5.9%)	18 (7.4%)	11 (5.3%)	.56
Number of other chronic diseases, mean (SD)	1.3 (1.2)	0.8 (1.0)	0.9 (1.2)	<.001	0.9 (1.1)	1.2 (1.3)	0.9 (1.1)	<.001
Use of beta-blockers, n (%)	52 (10.4%)	144 (6.8%)	33 (9.8%)	.008	188 (7.5%)	29 (11.9%)	12 (5.8%)	.03
Use of other heart medication, n (%)	62 (12.4%)	219 (10.4%)	37 (11.0%)	.40	287 (11.1%)	29 (11.9%)	11 (5.3%)	.03
Time of awakening, mean (SD)	7h23 (1h01)	7h27 (1h02)	7h37 (1h11)	.007	7h26 (1h02)	7h34 (1h01)	7h37 (1h06)	.02
Working on sampling day, n (%)	321 (64.5%)	1,550 (73.4%)	228 (67.7%)	<.001	1,773 (71.0%)	168 (69.1%)	158 (76.0%)	.24
Month with more daylight, n (%)	350 (70.3%)	1,442 (68.3%)	225 (66.8%)	.54	1,699 (68.1%)	170 (70.0%)	148 (71.2%)	.57
Sleep (≤6h of sleep), n (%)	142 (28.5%)	493 (23.3%)	95 (28.2%)	.02	594 (23.8%)	76 (31.3%)	60 (28.8%)	.01
Depression/anxiety-related characteristics								
Depressive disorder				<.001				<.001
No, n (%)	131 (26.3%)	750 (35.5%)	115 (34.1%)		916 (36.7%)	42 (17.3%)	38 (18.3%)	
Remitted, n (%)	105 (21.1%)	511 (24.2%)	76 (22.6%)		580 (23.2%)	69 (28.4%)	43 (20.7%)	
Current, n (%)	262 (52.6%)	851 (40.3%)	146 (43.3%)		1,000 (40.1%)	132 (54.3%)	127 (61.1%)	
Anxiety disorder				<.001				<.001
No, n (%)	152 (30.5%)	907 (42.9%)	136 (40.4%)		1,070 (42.9%)	69 (28.4%)	56 (26.9%)	
Remitted, n (%)	60 (12.0%)	298 (14.1%)	45 (13.4%)		352 (14.1%)	30 (12.3%)	21 (10.1%)	
Current, n (%)	286 (57.4%)	907 (42.9%)	156 (46.3%)		1,074 (43.0%)	144 (59.3%)	131 (63.0%)	
Use of SSRI, n (%)	138 (27.7%)	308 (14.6%)	58 (17.2%)	<.001	409 (16.4%)	49 (20.2%)	46 (22.1%)	.05
Use of TCA, n (%)	28 (5.6%)	40 (1.9%)	9 (2.7%)	<.001	64 (2.6%)	11 (4.5%)	2 (1.0%)	.06
Use of other antidepressants, n (%)	42 (8.4%)	110 (5.2%)	14 (4.2%)	.009	141 (5.6%)	15 (6.2%)	10 (4.8%)	.82
Alcohol use								
Alcohol use (drinks/day), mean (SD)	0.0 (0.0)	0.8 (0.7)	4.0 (1.8)	<.001	0.8 (1.1)	1.3 (1.8)	2.8 (2.3)	<.001

DISCUSSION

The present study shows that alcohol use, rather than alcohol dependence (AD), is associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis as well as the autonomic nervous system (ANS). On the one hand, we found that persons with a remitted or current AD did not differ from persons without a lifetime diagnosis of AD on any of the HPA-axis and ANS indicators. On the other hand, heavy alcohol use was associated with hyperactivity of the HPA-axis and increased sympathetic control of the heart compared to moderate alcohol use. The presence of AD did not change the association of alcohol use with both stress systems as similar patterns of HPA-axis activity and cardiac parasympathetic/sympathetic control across alcohol use groups were found in persons with and without lifetime AD.

To our knowledge, this study is the first to examine the relative contribution of alcohol use and AD to the HPA-axis and ANS. Previous studies have shown that heavy alcohol use was associated with hyperactivity of the HPA-axis (Adam et al., 2006; Badrick et al., 2008; Gianoulakis et al., 2003; Thayer et al., 2006) and increased sympathetic control of the ANS (Ohira et al., 2009; Ryan and Howes, 2002) in persons without AD. The present study corroborates these findings, but also provides important additional evidence as we found similar associations with alcohol use in persons without as well as with a lifetime diagnosis of AD. In our sample, alcohol use, and not AD, is associated with dysregulation of the HPA-axis and ANS and may account for the various physiological, psychological and behavioral problems -such as cardiovascular disease, depressive/ anxiety disorders and aggressive behavior- that are related to alcohol.

As findings of previous studies suggested that persons with AD have impaired inhibitory control, resulting in a blunted cortisol response and lower parasympathetic control of the ANS (Bar et al., 2006; Bernardy et al., 1996; Errico et al., 1993; Ingjaldsson et al., 2003; Kahkonen and Bondarenko, 2000; Lovallo et al., 2000; Rechlin et al., 1996; Thayer et al., 2006), whereas we did not find such an association, this may imply that the HPA-axis and ANS are only dysregulated in specific subgroups of alcohol dependent persons. Possibly, the extent of dysregulation may depend on the severity of the underlying addictive process, as was also suggested by others (Junghanns et al., 2003; Sinha et al., 2009). Therefore, our study provides important, additional information as we included a sample of regular alcohol dependent persons who have not been addressed in previous studies among severely dependent inpatients. We, therefore, conclude that there are no dysregulations of stress systems in non-treatment seeking alcohol dependent persons, although we cannot rule out that severely alcohol dependent inpatients may differ from our sample in this respect.

Table 1 Sample characteristics
Abbreviations: SSRI = Selective serotonin re-uptake inhibitors; TCA = tricyclic antidepressants. [a] p-value based on X^2-statistics (dichotomous and categorical variables) or analysis of variance (continuous variables).

	Alcohol use					Alcohol dependence (AD)				
	No		Moderate	Heavy		No	Remitted		Current	
	Mean (SE)	p[a]	Mean (SE)	Mean (SE)	p[b]	Mean (SE)	Mean (SE)	p[c]	Mean (SE)	p[d]
HPA-axis			(reference)			(reference)				
CAR: AUCg, nmol/l/h										
Unadjusted	18.6 (0.4)	.47	18.9 (0.2)	20.8 (0.5)	<.001	18.9 (0.2)	20.0 (0.6)	.08	20.4 (0.7)	.04
Adjusted[e]	18.8 (0.4)	.75	19.0 (0.2)	20.3 (0.5)	.02	19.0 (0.2)	19.3 (0.6)	.70	19.3 (0.7)	.68
CAR: AUCi, nmol/l/h										
Unadjusted	2.6 (0.4)	.28	2.1 (0.2)	3.0 (0.5)	.07	2.2 (0.2)	2.3 (0.5)	.94	2.6 (0.6)	.58
Adjusted[e]	2.6 (0.4)	.21	2.1 (0.2)	2.9 (0.5)	.11	2.3 (0.2)	2.1 (0.5)	.79	2.0 (0.6)	.67
Evening cortisol, nmol/l/h										
Unadjusted	4.6 (1.0)	.68	4.6 (1.0)	5.5 (1.0)	<.001	4.6 (1.0)	5.2 (1.0)	.01	5.3 (1.0)	.006
Adjusted[e]	4.8 (1.0)	.29	4.6 (1.0)	5.0 (1.0)	.006	4.7 (1.0)	4.7 (1.0)	.67	4.8 (1.0)	.65
Cortisol suppression ratio										
Unadjusted	2.3 (1.0)	.04	2.4 (1.0)	2.3 (1.0)	.03	2.4 (1.0)	2.3 (1.0)	.33	2.4 (1.0)	.61
Adjusted[e]	2.3 (1.0)	.07	2.4 (1.0)	2.3 (1.0)	.18	2.4 (1.0)	2.4 (1.0)	.86	2.4 (1.0)	.76
ANS			(REF)			(REF)				
Parasympathetic control										
RSA, ms										
Unadjusted	40.6 (1.2)	<.001	46.1 (0.6)	39.7 (1.4)	<.001	44.4 (0.5)	42.3 (1.7)	.24	47.6 (1.8)	.08
Adjusted[e]	42.7 (1.0)	.05	44.9 (0.5)	43.8 (1.2)	.37	44.2 (0.4)	45.7 (1.7)	.33	45.2 (1.5)	.54
Parasympathetic/sympathetic control										
HR, bpm										
Unadjusted	73.4 (0.4)	<.001	71.6 (0.2)	72.0 (0.5)	.56	72.1 (0.2)	71.5 (0.6)	.32	71.3 (0.7)	.26
Adjusted[e]	72.9 (0.4)	.006	71.6 (0.2)	72.7 (0.5)	.04	72.0 (0.2)	72.2 (0.6)	.78	71.8 (0.6)	.82
Sympathetic control										
PEP, ms										
Unadjusted	120.9 (0.8)	.16	119.6 (0.4)	118.5 (1.0)	.34	119.5 (0.4)	121.2 (1.3)	.22	120.0 (1.2)	.69
Adjusted[e]	121.2 (0.8)	.08	119.6 (0.4)	117.5 (1.0)	.04	119.7 (0.4)	119.5 (1.3)	.89	119.2 (1.2)	.64

Table 2 Results of Analyses of Covariance associating alcohol use and alcohol dependence with HPA-axis and ANS activity
Abbreviations: CAR = Cortisol Awakening Response, AUCg/i = Area under the curve with respect to the ground/increase, RSA = respiratory sinus arrhythmia, HR = heart rate, PEP = pre-ejection period.
[a] p-value comparing No versus Moderate alcohol use. [b] p-value comparing Heavy versus Moderate alcohol use.
[c] p-value comparing Remitted versus No AD. d p-value comparing Current versus No AD.

The current study has both strengths and limitations. The main strengths are the relatively large sample size and the presence of persons with and without AD, who also differed in their level of alcohol use. In addition, we examined the HPA-axis as well as ANS, which is unique in studies on alcohol use and AD. In contrast with previous studies, our study was also sufficiently powered to examine confounding by socio-demographics, health indicators and depression/anxiety-related characteristics. However, an important limitation of our study is that alcohol use and the presence of AD were based on self-report only. In addition, alcohol use and current AD were based on a longer time frame (last 12 months) than in other studies, limiting conclusions with regard to the temporal relationship between stress indicators and the level of alcohol use or status of AD to the very moment they were assessed. With regard to the cortisol suppression ratio, it is impossible to guarantee ingestion of the dexamethasone pill by all persons. Therefore, within a small validation study we had measured dexamethasone levels with a radioimmunoassay using the anti-dexamethasone antibody from IgG Corporation (Nashville, TN, functional detection limit is 0.4 nmol/l and reported cross-reactivity for cortisol is 0.04%) among a subset of 47 participants with a T1/T7 ratio <1.5 (indicative of non-suppression) who reported dexamethasone ingestion. We found detectable dexamethasone levels (>0.4 nmol/l) in the T7 saliva samples among 90%, indicating that non-compliance with dexamethasone ingestion is not likely to be frequent.

In conclusion, our sample consisted of persons with and without AD who also differed in their level of alcohol use and we could, therefore, determine the relative contribution of both alcohol use and AD on the HPA-axis and ANS. Heavy alcohol use, and not AD, was associated with dysregulations of both stress systems resulting in hyperactivity of the HPA-axis and increased sympathetic control of the heart. Consequently, dysregulations in both stress systems may explain the harmful physiological, psychological and behavioral consequences as seen in heavy drinkers.

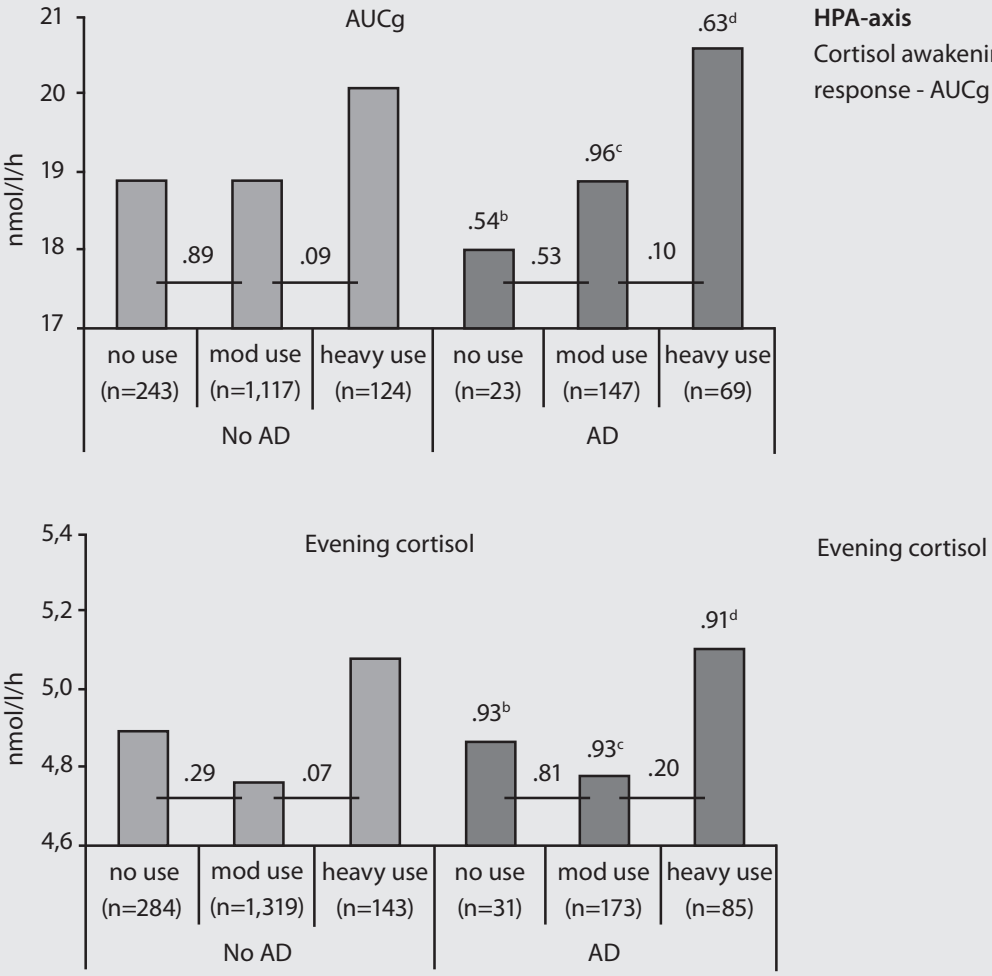
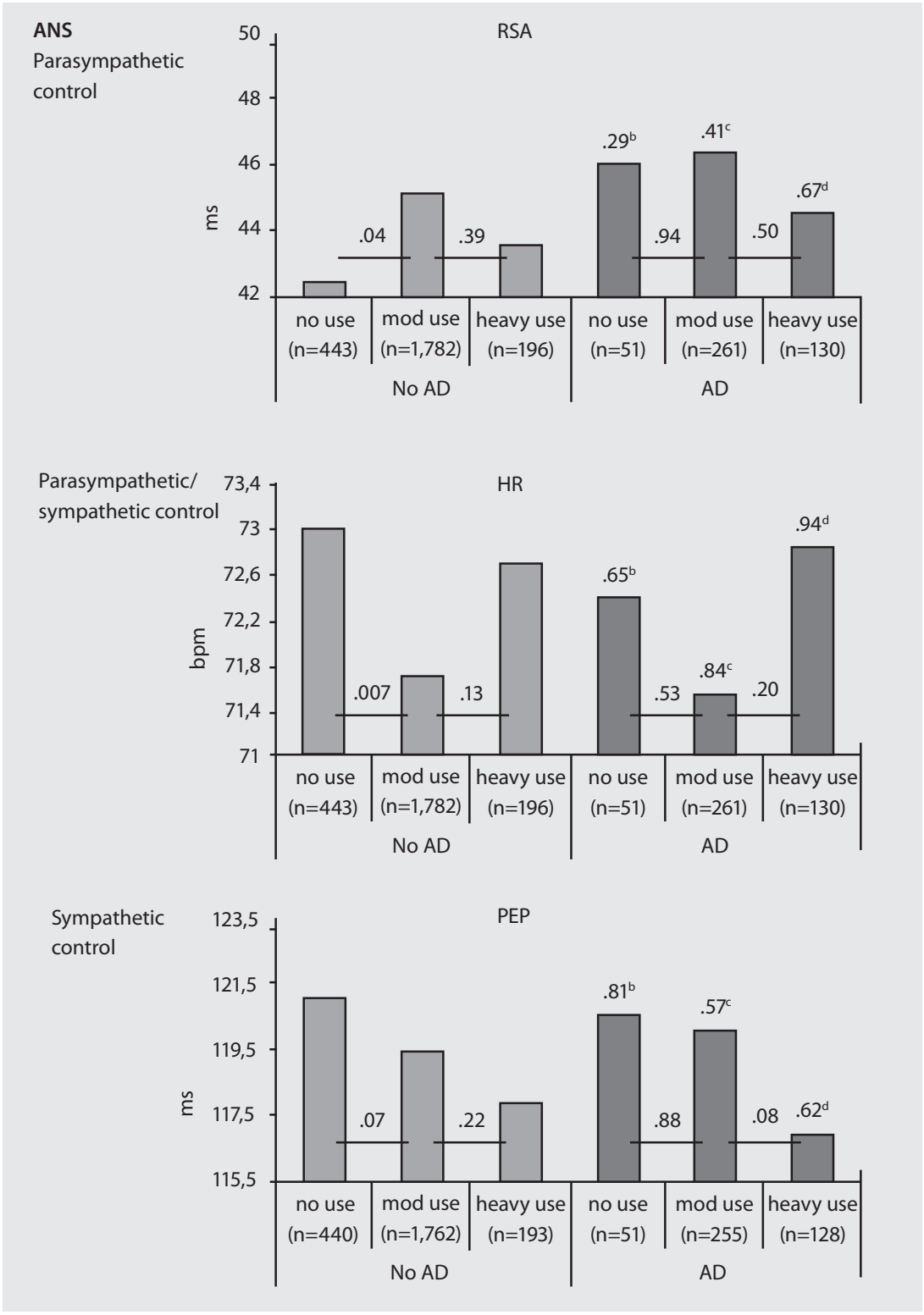


Figure 1 Results of Analyses of Covariance associating alcohol use and presence of AD with HPA-axis and ANS activity.[a]
Abbreviations: AUCg = Area under the curve with respect to the ground, RSA = respiratory sinus arrhythmia, HR = heart rate, PEP = pre-ejection period.
[a] Adjusted for sex, age, education, BMI, physical activity, heart disease, number of other chronic diseases, use of beta blockers, use of other heart medication, past or current smoking, presence of a remitted or current depressive or anxiety disorder and use of TCA, SSRI or other antidepressants. For HPA axis, analyses are additionally adjusted for working status, time of awakening, month with more daylight and sleep.
[b]Comparing non-drinkers with AD versus without AD.
[C]Comparing moderate drinkers with AD versus without AD.
[d]Comparing heavy drinkers with AD versus without AD.


ANS
Parasympathetic control
RSA
ms
50
48
46
44
42
.04
.39
.29b
.94
.41c
.50
.67d
no use (n=443)
mod use (n=1,782)
heavy use (n=196)
no use (n=51)
mod use (n=261)
heavy use (n=130)
No AD
AD
Parasympathetic/ sympathetic control
HR
bpm
73,4
73
72,6
72,2
71,8
71,4
71
.007
.13
.65b
.53
.84c
.20
.94d
no use (n=443)
mod use (n=1,782)
heavy use (n=196)
no use (n=51)
mod use (n=261)
heavy use (n=130)
No AD
AD
Sympathetic control
PEP
ms
123,5
121,5
119,5
117,5
115,5
.07
.22
.81b
.88
.57c
.08
.62d
no use (n=440)
mod use (n=1,762)
heavy use (n=193)
no use (n=51)
mod use (n=255)
heavy use (n=128)
No AD
AD

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